

General

Guideline Title

2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia.

Bibliographic Source(s)

Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, Pillinger MH, Merill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Liote F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012 Oct;64(10):1431-46. [73 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): The American College of Rheumatology (ACR) guidelines for management of gout focus on 4 specific domains in gout management. Two of these domains are addressed herein, i.e., urate-lowering therapy (ULT) and chronic gouty arthritis with tophaceous disease detected on physical examination (designated by the ACR with the terminology "chronic tophaceous gouty arthropathy" [CTGA] and specifically represented in the fundamental case scenarios 7–9 described herein). The remaining 2 domains (analgesic and antiinflammatory management of acute gouty arthritis and pharmacologic antiinflammatory prophylaxis of attacks of gouty arthritis) are addressed in part 2 of the guidelines as a separate article (see the NGC summary of the ACR guideline [2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis](#)).

The levels of evidence supporting the recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Primary Principles of Management for All Gout Case Scenarios

The task force panel (TFP) generated recommendations for a systematic nonpharmacologic and pharmacologic management approach intended to be applicable to all patients with gout, which is summarized in Figure 3 in the original guideline document. This was based on the assumption that the diagnosis of gout was correct before initiation of management. The approach highlighted patient education on the disease and treatments and their objectives, and initiation of diet and lifestyle recommendations, including the particular role of uric acid excess in gout and as the key long-term treatment target (evidence B). The TFP also recommended, on a case-by-case basis, careful consideration of potential elimination of serum

urate-elevating prescription medications that might be nonessential for the optimal management of comorbidities (e.g., hypertension, hyperlipidemia, or major organ transplant) in a given patient. Prime examples of urate-elevating medications are thiazide and loop diuretics, niacin, and calcineurin inhibitors (evidence C). However, the TFP, without a specific vote, recognized the particular benefits of thiazides for blood pressure control and outcomes in many patients with hypertension. Although low-dose acetylsalicylic acid (aspirin ≤ 325 mg daily) elevates serum urate, the TFP did not recommend discontinuation of this modality as cardiovascular disease prophylaxis in gout patients. In discussion, without a specific vote, the TFP viewed the relative risks specifically attributable to the modest effects of low-dose aspirin on serum urate as negligible in gout management.

The TFP recommended that clinicians consider causes of hyperuricemia for all gout patients, and recommended a specific comorbidity checklist (evidence C) (see Table 2 in the original guideline document). In doing so, the TFP specially recommended consideration, and if indicated, medical evaluation of certain agents and disorders that cause uric acid underexcretion or overproduction, which thereby could merit laboratory investigations such as urinalysis, renal ultrasound, a complete blood cell count with differential cell count, or urine uric acid quantification, as indicated. In this context, the TFP specifically recommended screening for uric acid overproduction (by urine uric acid evaluation) in patient subsets with gout clinical disease onset before age 25 years (evidence C) or a history of urolithiasis (evidence C).

The TFP provided guidance for referral to a specialist, with caution to avoid appearing self-serving. Although limited by the absence of outcomes data on potential benefits of referral, the TFP recommended that gout case scenarios including any of the following should be among those where referral to a specialist is considered (evidence C for all): 1) unclear etiology of hyperuricemia; 2) refractory signs or symptoms of gout; 3) difficulty in reaching the target serum urate level, particularly with renal impairment and a trial of xanthine oxidase inhibitor (XOI) treatment; and 4) multiple and/or serious adverse events from pharmacologic ULT.

Clinical Evaluation of Gout Disease Activity and Burden

The TFP recommended clinical evaluation of gout disease symptom severity and burden in individual patients by history and a thorough physical examination for symptoms of arthritis and signs such as tophi and acute and chronic synovitis (evidence C). To be actionable by clinicians, the authors without a specific TFP vote suggested that clinicians can work with patients to record and estimate the number per year and severity of acute attacks of gouty arthritis per year.

Core Recommendations for Nonpharmacologic ULT Measures in Gout

The TFP recommended certain diet and lifestyle measures for the majority of patients with gout (evidence B and C for individual measures) (see Figure 4 in the original guideline document). Many of the diet and lifestyle measures were recommended for decreasing the risk and frequency of acute gout attacks and lowering serum urate levels, but the primary emphasis of the TFP recommendations in Figure 4 of the original guideline document was on diet and lifestyle choices for promotion and maintenance of ideal health and prevention and optimal management of life-threatening comorbidities in gout patients, including coronary artery disease and obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, and hypertension.

Dietary recommendations were grouped into 3 simple qualitative categories, termed "avoid," "limit," or "encourage" (see Figure 4 in the original guideline document). This approach, with rare exceptions, reflected a general lack of specific evidence from prospective, blinded, randomized clinical intervention trials that linked consumed quantities of individual dietary components to changes in either serum urate levels or gout outcomes. Notably, the replication of hazardous lifestyle risk factors in a conventional clinical research trial would potentially pose both design and ethical difficulties. As such, the TFP deliberated on evidence regarding the impact of exposures to alcohol or purine-rich foods in a short timeframe. The evidence sources were epidemiologic studies of hyperuricemia and incident gout, including long-term prospective analyses and internet-based case-crossover studies of specific exposures. The TFP recommended that gout patients limit their consumption of purine-rich meat and seafood (evidence B) as well as high fructose corn syrup-sweetened soft drinks and energy drinks (evidence C), and encouraged the consumption of low-fat or nonfat dairy products (evidence B) (see Figure 4 in the original guideline document). The TFP voted to encourage vegetable intake in gout patients (evidence C) (see Figure 4 in the original guideline document), having considered evidence in healthy subjects for lowered serum urate levels and urine urolithiasis risk factors associated with dietary vegetable intake. However, there was no specific TFP vote on the question of avoidance of excess purine intake from food sources other than meat and seafood, such as vegetables and legumes, in gout patients. The TFP recommended reduced consumption of alcohol (particularly beer, but also wine and spirits) and avoidance of alcohol overuse in all gout patients (evidence B) (see Figure 4 in the original guideline document). The TFP further recommended abstinence from alcohol consumption for gout patients during periods of active arthritis, especially with inadequate medical control of the disorder and in CTGA (evidence C). Significantly, in discussion by the TFP, without a specific vote, the TFP recognized that diet and lifestyle measures alone provide therapeutically insufficient serum urate-lowering effects and/or gout attack prophylaxis for a large fraction of individuals with gout. For example, some clinical trials on diet and fitness have reported only an approximately 10%–18% decrease in serum urate. In further discussion by the TFP, again without a specific vote, the TFP viewed this degree of serum urate level lowering as beneficial for all case scenarios, but insufficient to achieve an effective serum urate target in those with sustained hyperuricemia substantially above 7 mg/dL.

Core Recommendations for Pharmacologic ULT, Including the Serum Urate Target

Here, and with all other recommendations for drug therapy in parts 1 and 2 of the 2012 ACR guidelines for gout, the recommendations assumed a lack of contraindications, intolerance, serious adverse events, or drug–drug interactions for given agents. The TFP recommended gout with chronic kidney disease (CKD) stage 2–5 or endstage renal disease as an appropriate indication, by itself, for pharmacologic ULT (evidence C) in patients with prior gout attacks and current hyperuricemia. In pharmacologic ULT, certain treatment choices (e.g., probenecid) and drug dosing decisions (e.g., allopurinol) are impacted by the creatinine clearance. The TFP, without a direct vote, discussed and recognized the clinical value of accurate measurement of creatinine clearance, not simply the serum creatinine, in ascertaining the degree of renal impairment. However, the scope of the project did allow for detailed prescriptive recommendations regarding specific ULT drug doses, usage of individual agents in the presence of a given degree of either renal impairment, or other comorbidities such as hepatic impairment.

TFP recommendations for pharmacologic ULT, shown graphically in Figure 3 of the original guideline document, included recommendation of XOI therapy with either allopurinol or febuxostat as the first-line pharmacologic approach (evidence A). The panel did not preferentially recommend either XOI over the other XOI drug. In doing so, the TFP weighed the lack of published safety data for febuxostat in the setting of stage 4 or worse CKD. Probenecid was recommended as an alternative first-line pharmacologic ULT option in the setting of contraindication or intolerance to at least 1 XOI agent (evidence B). However, the TFP did not recommend probenecid as a first-line ULT monotherapy in those with a creatinine clearance below 50 ml/minute.

The TFP recommended that pharmacologic ULT could be started during an acute gout attack, provided that effective antiinflammatory management has been instituted (evidence C). The TFP recommended regular monitoring of serum urate (every 2–5 weeks) during ULT titration, including continuing measurements once the serum urate target is achieved (every 6 months; evidence C). The TFP weighed this measure as particularly useful to monitor adherence, given that poor adherence to ULT is a common problem in gout patients.

The TFP recommended that the goal of ULT is to achieve a serum urate level target at a minimum of <6 mg/dl in all gout case scenarios (evidence A). Moreover, the TFP recommended that the target serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, including palpable and visible tophi detected by physical examination, and that this may involve therapeutic serum urate level lowering to below 5 mg/dl (evidence B).

Recommendations Specific to Allopurinol Dosing and Pharmacogenetics

TFP recommendations for use of allopurinol in gout are summarized in Table 3 in the original guideline document. Importantly, the TFP recommended that the starting dosage of allopurinol should be no greater than 100 mg per day (evidence B), consistent with prior Food and Drug Administration (FDA) and European League Against Rheumatism (EULAR) guidelines. The rationale of the TFP was partly that a low allopurinol starting dose could reduce early gout flares after ULT initiation, and partly as a component of risk management with respect to the potential for severe hypersensitivity reaction to allopurinol, discussed in further detail below. The TFP recommended gradual upward titration of the allopurinol maintenance dose every 2–5 weeks to an appropriate maximum dose for gout, in order to treat to the serum urate target appropriate for the individual patient (evidence C).

The TFP weighed robust evidence that allopurinol monotherapy at doses of 300 mg or less daily failed to achieve the serum urate level target of <6 mg/dl or <5 mg/dl in more than half of the subjects with gout. The TFP reviewed small studies in which the allopurinol dose was titrated above 300 mg daily in gout with overall success in achieving the serum urate target. Importantly, in doing so, the TFP also recommended that the maintenance dosage of allopurinol can be raised above 300 mg per day, even in those with renal impairment, provided there is adequate patient education and regular monitoring for drug hypersensitivity and other adverse events, such as pruritis, rash, and elevated hepatic transaminases, as well as attention to potential development of eosinophilia (evidence B).

The TFP next considered the issue of measures to reduce the incidence of severe allopurinol hypersensitivity reactions, here termed allopurinol hypersensitivity syndrome (AHS). TFP discussion recognized the potential for hospitalization and severe morbidity and the reported mortality rate of 20%–25% in AHS. The estimated incidence of AHS is approximately 1:1,000 in the U.S., and its spectrum includes not only Stevens-Johnson syndrome and toxic epidermal necrolysis, but also systemic disease with a clinical constellation of features such as eosinophilia, vasculitis, rash, and major end-organ disease. Concurrent thiazide use and renal impairment have been implicated as risk factors for AHS. A widely employed risk management strategy has been a non-evidence-based algorithm for allopurinol maintenance dosing, calibrated to renal impairment (evidence C); importantly, the TFP did not recommend this strategy.

In their evaluation of the allopurinol starting dose as a component of risk management strategy, the TFP first weighed evidence that the highest risk of severe allopurinol hypersensitivity reaction is in the first few months of therapy. A recent case–controlled retrospective analysis of AHS and allopurinol starting dose further supported the aforementioned recommendation by the TFP of a starting dose of allopurinol of no more than 100 mg daily, and the TFP recommendation of an even lower starting dose of allopurinol (50 mg daily) in stage 4 or worse CKD (evidence B).

The TFP also weighed the rapidly emerging area of pharmacogenetics to screen for AHS, and recommended that, prior to initiation of allopurinol, human leukocyte antigen (HLA)–B*5801 testing should be considered in select patient subpopulations at an elevated risk for AHS (evidence A). Those with HLA–B*5801 and of Korean descent with stage 3 or worse CKD (HLA–B*5801 allele frequency approximately 12%), or of Han Chinese or Thai extraction irrespective of renal function (HLA–B*5801 allele frequency approximately 6%–8%), have been highlighted in the literature as prime examples of subjects at high risk for AHS, marked by HLA–B*5801 hazard ratios of several hundred. Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA–B*5801 positive (evidence A). The TFP recommended that the HLA–B*5801 screening be done by the rapid, widely available polymerase chain reaction (PCR)–based approach (evidence A) that, in only approximately 10% of tests, requires more cumbersome followup HLA–B*5801 sequencing for inconclusive results. Significantly, the TFP did not recommend universal HLA–B*5801 allopurinol screening. Current evidence informing this TFP decision included that whites with an HLA–B*5801 prevalence of approximately 2% had a substantially lower HLA–B*5801 hazard ratio and negative predictive value of the test than in the aforementioned Asian subpopulations.

Recommendations Specific to Primary Uricosuric Urate-Lowering Monotherapy

Under conditions where uricosuric monotherapy was employed as a primary ULT modality (see Table 3 in the original guideline document), probenecid was recommended by the TFP as the first choice among uricosuric drugs currently available in the U.S. (evidence B). The TFP recommended that a history of urolithiasis contraindicates first-line use of a potent uricosuric agent for ULT (evidence C), given that probenecid (and benzbromarone, which is unavailable in the U.S.) was associated with an approximately 9%–11% risk of urolithiasis. Specific TFP recommendations for risk management in uricosuric ULT also included initial measurement and monitoring of urine uric acid, and that an elevated urine uric acid level indicative of uric acid overproduction contraindicates uricosuric ULT. There was no TFP consensus on assay of undissociated urine uric acid, or use of Simkin's Index and similar calculation on spot urine, in risk management in uricosuric therapy. The TFP did recommend that when initiating uricosuric ULT, patients should also be instructed to increase fluid intake and consider urine alkalinization (e.g., with potassium citrate; evidence C for all), but no quantitative parameters were voted on for these measures, in view of lack of evidence.

Recommendations on Pharmacologic ULT Decision Making in Gout, Including Case Scenarios with Mild, Moderate, or Severe Disease Activity or CTGA

The TFP voted on clinical decision making in each of the 9 case scenarios when the serum urate target had not yet been met and under circumstances where gout remained symptomatic (i.e., where there were 1 or more continuing clinical signs and symptoms of gout, such as recent acute gout attacks, tophi, and chronic gouty arthritis) (see Figure 5 and Table 4 in the original guideline document). In doing so, the TFP, in limited voting scenarios, first considered the potential role of imaging in the evaluation of disease burden and clinical decision making on ULT gout. The TFP recommended the utility of high-resolution ultrasound, computed tomography (CT), or dual-energy CT (evidence B) to detect tophi, and the utility of plain radiographic findings consistent with tophi (such as characteristic bone erosion; evidence C). The TFP also voted that the ultrasound "double contour sign" was consistent with nontophaceous urate crystal deposition on the surface of articular cartilage (evidence B). However, the TFP did not recommend use of the double contour sign as a sufficient indicator for initiating or increasing the intensity of ULT, given that the sign was detected in joints of approximately 25% of subjects with asymptomatic hyperuricemia in a recent study. Conversely, in a recent study, the double contour sign was not universally detectable (i.e., absent in approximately 33% of subjects in an ultrasound survey of multiple joints in each subject) in patients with early gout not receiving ULT.

For all 9 case scenarios when the serum urate target has not been met, the TFP recommended upward dose titration of 1 XOI (allopurinol or febuxostat) to the respective maximum appropriate dose for the individual patient (evidence A) (see Figure 5 and Table 4 in the original guideline document). The maximum FDA-approved dose of allopurinol is 800 mg daily, and for febuxostat is 80 mg daily. Given the request for an international frame of the gout guidelines by the ACR, the TFP recommended increasing febuxostat up to 120 mg daily, a dose approved in many countries outside the U.S., in the specific scenario of active disease refractory to appropriately dosed oral ULT (evidence A). The TFP further recommended, and broadly so in the 9 case scenarios, that if upward titration of the initial XOI agent was not tolerated or did not achieve the serum urate target, substitution of another XOI was an appropriate first-line option (evidence C).

Notably, the TFP recommended probenecid and other agents with clinically significant uricosuric effects, such as fenofibrate and losartan, as therapeutically useful in a comprehensive ULT program in refractory disease (evidence B). Specifically, the TFP recommended a combination oral ULT approach (i.e., 1 XOI agent [allopurinol or febuxostat] and 1 uricosuric agent [probenecid, fenofibrate, or losartan being the currently available agents in the U.S.]) as an option when the serum urate target has not been met across the 9 case scenarios (evidence B) (see Figure 5 and Table 4 in the original guideline document).

Last, the TFP recommended pegloticase as appropriate only in the case scenarios with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options (evidence A) (see Figure 5 and Table 4 in the original guideline document). In 2 large placebo-controlled randomized clinical trials, pegloticase 8 mg every 2 weeks was effective in reducing the serum uric acid level to <6 mg/dl in 42% of patients versus 0% in the placebo group at 6 months. In addition, 45% of patients receiving pegloticase 8 mg every 2 weeks had complete

resolution of 1 or more tophi versus 8% in the placebo group, with significant improvement in chronic arthropathy and health-related quality of life. Importantly, the TFP did not recommend pegloticase as a first-line ULT for any case scenarios. The TFP also did not achieve consensus on the appropriate duration of pegloticase therapy once decreased symptoms and signs of gout, including decrease in size (or resolution) of tophi on clinical examination, had been achieved.

Definitions:

Level of Evidence

Level A: Recommendations supported by multiple (i.e., >1) randomized clinical trials or meta-analyses

Level B: Recommendations derived from a single randomized trial or nonrandomized studies

Level C: Consensus opinion of experts, case studies, or standard of care

Clinical Algorithm(s)

The original guideline document provides a clinical algorithm for baseline recommendations and overall strategic plan for patients with gout.

Scope

Disease/Condition(s)

Gout

Other Disease/Condition(s) Addressed

- Chronic kidney disease
- Hyperlipidemia
- Hypertension
- Type 2 diabetes mellitus (T2DM)
- Urolithiasis

Guideline Category

Counseling

Evaluation

Management

Prevention

Screening

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Medical Genetics

Nephrology

Nutrition

Rheumatology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Dietitians

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To develop systematic nonpharmacologic and pharmacologic recommendations for effective treatments in gout with an acceptable risk/benefit ratio and applicable to all patients with gout
- To reflect best practice, as evaluated by a diverse group of experts that examined the level of evidence available at the time

Target Population

Patients with gout

Interventions and Practices Considered

Diagnosis/Assessment

1. Assessment of comorbidities
2. Assessment of use of urate-elevating medicines
3. Laboratory investigations, as indicated, e.g., urinalysis, renal ultrasound, a complete blood cell count with differential cell count, or urine uric acid quantification
4. Referral to a specialist, as indicated
5. History and physical examination for symptoms of arthritis and signs such as tophi and acute and chronic synovitis
6. Imaging: high-resolution ultrasound, computed tomography (CT), dual-energy CT, or plain radiographs, as indicated

Management/Counseling/Treatment

1. Patient counseling on diet, weight loss, exercise, reduction in alcohol use, and fluid intake
2. First-line treatment with allopurinol or febuxostat
3. Probenecid as alternative first-line therapy for patients with a contraindication to a xanthine oxidase inhibitor (XOI), depending on creatinine clearance
4. Uricosuric monotherapy with probenecid, fenofibrate, or losartan
5. Timing of treatment initiation
6. Frequency of urate monitoring during drug titration
7. Measurement of human leukocyte antigen (HLA)–B*5801 in patients at risk of allopurinol hypersensitivity syndrome (AHS)

8. Urine alkalinization (e.g., with potassium citrate) during uricosuric monotherapy
9. Combination therapy (e.g., with an XOII and a uricosuric agent) in refractory cases
10. Pegloticase only in severe gout disease and refractoriness to, or intolerance to oral urate-lowering medicines (not recommended as first-line therapy for any patient)

Major Outcomes Considered

- Risk and frequency of gout attacks
- Changes in serum urate levels
- Tophus size
- Efficacy of treatment in achieving serum urate target
- Time to treatment response
- Adverse effects of treatment
- Health-related quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The search of PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from the 1950s to the present for articles on gout, used a search strategy based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials, and search terms related to gout, hyperuricemia, tophi, and arthritis, described in the text. Limits included English Language and the exclusion of "animal only" studies. The exact search terms included: ("gout"[mh] OR gout*[tw] OR "Hyperuricemia"[mh] OR hyperuricemia[tw] OR hyperuricaemia[tw] OR toph*[tw] OR arthritis uric*[tw] OR arthritis uric*[tw] OR uric acid dis*[tw]) AND English[lang] NOT ("animals"[MeSH] NOT "humans"[MeSH]). The first search (9/25/10) retrieved 5,380 articles from PubMed and CENTRAL. As schematized, the review was divided into three stages: titles, abstracts, and manuscripts. Each phase required two team members to assess the items individually for relevancy, and items were rejected if they fulfilled explicit exclusion criteria, such as studies not done in gout patients. Discordant assessments between reviewers were resolved with direct discussion between the two raters. Remaining disagreements were adjudicated by a third party arbitrator. Of the 5,830 titles, 192 duplicate titles and 82 non-English titles were excluded, with an additional 3,729 titles excluded based on pre-defined criteria – leaving 1,827 titles, of which another 1,699 were excluded in the manuscript abstract review phase. Of the 128 manuscripts reviewed, there were 41 eligible manuscripts on non-pharmacologic measures (such as diet and alcohol, etc.) in gout patients, but none were randomized, controlled trials and all were excluded. The remaining 87 manuscripts met the inclusion criteria for pharmacologic agents in gout patients, but 40 of these were excluded because they were not controlled trials. Subsequently, the systematic review was updated by repeating the search with the same criteria to include any articles that were published between 9/25/10 and 3/31/11. Recent meeting abstracts from the American College of Rheumatology and European League Against Rheumatism (EULAR) were searched for any randomized controlled trials that were yet to be published, before presentation to the Task Force Panel (TFP) in the evidence report. The supplemental search resulted in 4 additional manuscripts, and 5 meeting abstracts on pharmacologic agents. The gout literature was reviewed until April 20, 2012.

Number of Source Documents

A total of 51 manuscripts and 5 meeting abstracts were reviewed.

Methods Used to Assess the Quality and Strength of the Evidence

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level A: Recommendations supported by multiple (i.e., >1) randomized clinical trials or meta-analyses

Level B: Recommendations derived from a single randomized trial or nonrandomized studies

Level C: Consensus opinion of experts, case studies, or standard of care

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The RAND/University of California at Los Angeles (UCLA) method requires a core expert panel (CEP) that provides input into case scenario development and preparation of a scientific evidence report. The CEP consisted of leaders for each domain (see Supplemental Figure 2, available in the online version of this guideline at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) []).

Pharmacologic approaches and diet, lifestyle, and nonpharmacologic measures (e.g., weight loss, exercise) were addressed within each domain. Although a previous systematic review for gout has been performed by the European League Against Rheumatism (EULAR), as a prime example, a new systematic review of pertinent literature was performed.

The Core Expert Panel (CEP) performed its own systematic review of pertinent literature. The resultant scientific evidence report was given to the Task Force Panel (TFP) in conjunction with clinical scenarios representing differing degrees of disease activity (see the "Methods Used to Formulate the Recommendations" field). There were multiple questions of interest and alternative options presented for each case scenario.

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology and applied to recent American College of Rheumatology (ACR) recommendations.

Of the reviewed literature, 21 manuscripts were on urate-lowering therapy (ULT), and were presented to the TFP in the evidence report. Abstracts presented at ACR or EULAR meetings (including case series, single center trials) were graded as level C evidence, unless a multicenter randomized controlled trial. The majority of the meeting abstracts reviewed were subsequently published as full manuscripts in the open literature, with evidence level of these studies subsequently re-graded, as appropriate.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

Project Design and Development of Recommendations

The overall design of the project is schematized in Supplemental Figure 1 (available in the online version of the original guideline document at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) []). The RAND/University of California at Los Angeles (UCLA) consensus methodology, developed in the 1980s, incorporates both Delphi and nominal group methods, and was successfully used to develop other guidelines commissioned by the American College of Rheumatology (ACR). The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical

decision making. The RAND/UCLA method requires two groups of experts: a core expert panel (CEP) that provides input into case scenario development and preparation of a scientific evidence report, and a task force panel (TFP) that votes on these case scenarios. The CEP consisted of leaders for each domain (see Supplemental Figure 2, available in the online version of the guideline at

[http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). Pharmacologic approaches and diet, lifestyle, and nonpharmacologic measures (e.g., weight loss, exercise) were addressed within each domain. The CEP leaders communicated with an international panel of gout experts and the principal investigators to develop initial case scenarios that reflected broad differences in severity of the disease and its clinical manifestations. In addition, there were weekly interactive teleconferences between the domain leaders and principal investigators to refine case scenarios. The scientific evidence report was given to the TFP in conjunction with clinical scenarios representing differing degrees of disease activity. There were multiple questions of interest and alternative options presented for each case scenario.

By ACR mandate, the TFP had a majority of members without a perceived potential conflict of interest, and had diverse experience and expertise, as described in detail in Supplemental Figure 2 (available in the online version of this article at

[http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). The TFP included seven rheumatologists (including one Chair of Internal Medicine and one Internal Medicine Residency Training Program Director), two primary care physicians, a nephrologist, and a patient representative. There were two rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each of the potential elements of the guidelines on a risk/benefit basis ranging from 1–9 on a Likert scale using the Delphi process, followed by a face-to-face group discussion and then revoting of the same scenarios. A vote of 1–3 on the Likert scale was rated as *inappropriate* (risks clearly outweigh the benefits), a vote of 4–6 was considered *uncertain* (risk/benefit ratio is uncertain), and a vote of 7–9 was rated as *appropriate* (benefits clearly outweigh the risks). Samples of votes taken and results are provided in Supplemental Figure 3 (available in the online version of the original guideline document at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). Votes on case scenarios were translated into recommendations if the median voting score was graded 7–9 (appropriate) and if there was no significant disagreement, defined as no more than 1 of 3 of the votes graded as inappropriate for the scenario. The final rating was done anonymously in a two-day face-to-face meeting, facilitated by an experienced moderator. During the face-to-face TFP meeting, some case scenarios were clarified for content or verbiage and revoted on by the TFP.

Clinical Case Descriptions

The TFP evaluated clinical scenarios with differences in frequency of acute gout symptoms and differences related to the presence or extent of chronic findings (tophi, synovitis) on physical examination, similar to what a clinician might see in a busy practice. Scenarios were divided into mild, moderate, and severe disease activity in each of three distinct "treatment groups" (see Figures 1A and B in the original guideline document). In generating these nine fundamental clinical case scenarios, mild disease activity levels in each treatment group were meant to represent patients at the lowest disease activity level for which most clinicians would consider initiating or altering a specific medication regimen. Conversely, the severe disease activity level was intended to represent patients with disease activity greater than or equal to that of the "average" subject studied in a clinical trial. The case scenarios were not intended to serve as classification criteria. To allow the TFP to focus on management decisions, each case scenario had the assumption that the diagnosis of gout was correct. In addition, it was assumed that there was some clinical evidence of gout disease activity. This included intermittent symptoms of variable frequency, specifically presented to the TFP as episodes of acute gouty arthritis of at least moderate to severe pain intensity. Other clinical evidence of gout disease activity, presented to the TFP in specific case scenarios, was tophi detected by physical examination, or alternatively, chronic symptomatic arthritis (i.e., "chronic arthropathy" or "synovitis") due to gout, with or without confirmed joint damage (e.g., deformity, erosion due to gout on an imaging study) (see Figure 2 in the original guideline document). Hyperuricemia was defined here as a serum urate level >6.8 mg/dl. All aspects of case scenario definitions were determined by a structured iterative process, using regular e-mail and teleconferences at least once per month. Multiple revisions to the proposed parameters were carried out, until accepted by the CEP domain leaders.

Key Assumptions in the Process Applied to Develop the Recommendations

1. Recommendations were developed using the RAND/UCLA methodology, which assesses level of evidence and safety and quality, but does not take comparisons of cost and cost-effectiveness of therapies into consideration.
2. The guidelines focused on clinically-based decision making in common scenarios and not on rare case presentations.
3. Multiple scenarios were developed for acute treatment and chronic gout for voting purposes and are NOT meant to be disease classification criteria for gout.
4. The project did not list specific drug choices, contraindications, and dosing in the presence of comorbidities associated with gout or with potential drug–drug interaction. These decisions are left with the practitioner, based on evaluation of the risk/benefit ratio when prescribing each therapy, the drug dosing and safety labeling, and other widely available databases and accessible sources of general medical information about potential drug-related adverse events.
5. When a particular drug is not recommended, it does not imply that it is contraindicated. Similarly, if a hierarchy or sequence of a treatment is recommended, it does not necessarily imply that an agent lower in the hierarchy is contraindicated.

6. It is assumed that the diagnosis of gout was correct before initiation of any management option.
7. It is not always possible for the task force panel to reach a consensus on a case scenario (see Supplemental Figure 3 for examples of voting scenarios, available in the online version of the original guideline document at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

Definitions of Pharmacologic Therapeutic Agents

Medication classes evaluated in the case scenarios were defined as follows: xanthine oxidase inhibitor (XOI) refers to allopurinol or febuxostat, and uricosuric agents were defined to include agents available in the U.S. (probenecid and off-label use [as uricosuric therapy] of fenofibrate and losartan), but did not include sulfinpyrazone or benzbromarone. Other agents and modalities were self-explanatory. Evaluation by the TFP of effectiveness of a given therapeutic option assumed that patients in the case scenarios received the maximum tolerated typical dose for a period of time sufficient to accurately assess therapeutic response, unless otherwise indicated.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The RAND/University of California at Los Angeles (UCLA) methodology utilized for this project did not allow the guideline authors to address the important clinical practice and societal implications of treatment costs, which clearly impact patient and provider preferences for gout management options recommended by the task force panel (TFP) as effective. For example, the authors recognize the potential cost issues of the urate-lowering therapy (ULT) recommendations presented, since, for example, febuxostat is substantially more expensive than allopurinol or probenecid. The guideline authors note that a recent single technology appraisal with cost analysis done by an independent evidence review group of the National Institute for Health and Clinical Excellence concluded that febuxostat should be recommended for ULT in gout only in patients with contraindications or intolerance to allopurinol. Conversely, polymerase chain reaction (PCR)-based human leukocyte antigen (HLA)-B*5801 pharmacogenetics screening for allopurinol is a one-time test and relatively inexpensive, but raises new questions about the added costs to gout management, particularly for populations where the risk of allopurinol hypersensitivity syndrome (AHS) is low. Last, third-line ULT with pegloticase is an expensive biologic therapy approach for gout, and additional biologic agents for gout therapy are currently being developed and investigated. Cost-effectiveness trials and analyses are particularly timely for emerging therapies in gout.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Peer Review of Recommendations

After the draft recommendations were submitted, the American College of Rheumatology (ACR) invited peer review, prior to journal review, done by the ACR Practice Guidelines Subcommittee, the ACR Quality of Care Committee, and the ACR Board of Directors.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most of the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of gout using systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia

Potential Harms

Adverse effects of therapeutic agents

Contraindications

Contraindications

- History of urolithiasis contraindicates first-line uricosuric urate-lowering monotherapy.
- Elevated urine uric acid indicative of uric acid overproduction contraindicates uricosuric urate-lowering therapy (ULT).

Qualifying Statements

Qualifying Statements

- Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.
- Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included in these recommendations.
- Individual results of this work are designated as "recommendations" rather than guidelines, in order to reflect the nonprescriptive nature of decision making evaluated by experts and based on available evidence at the time. The recommendations cannot substitute for individualized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. Treatment recommendations also assume appropriate attention to potential drug interactions (e.g., with anticoagulants, azathioprine, amoxicillin) and effects of comorbidities such as diabetes mellitus and renal, cardiac, gastrointestinal, and hepatic disease (see Table 1 in the original guideline document). The motivation, financial circumstances, and preferences of the gout patient play a very important role in treatment choice. Moreover, the recommendations for gout management presented here are not intended to limit or deny third party payor coverage of health care costs for groups or individual patients with gout.

Limitations of the Guidelines

- Limitations include the quality and quantity of evidence evaluated. For part 1 of the gout guidelines, the majority of evidence reviewed, upon which recommendations were based, was level C, with less than 20% level A evidence. For urate-lowering therapy (ULT) clinical trials, study designs comparing allopurinol to febuxostat, where both agents are titrated to attempt to achieve the serum urate target, would be more informative than past trials.
- Another issue was variability in end points and outcome measures (e.g., gout attack frequency, serum urate, tophus size reduction, and health-related quality of life) in the clinical trials reviewed. Moreover, there are likely differences in "real-world" patients compared to those in most large industry-sponsored clinical trials. Clearly, further studies are needed in both the ULT and chronic tophaceous gouty arthropathy (CTGA) domains of gout.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, Pillinger MH, Merrill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Liote F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012 Oct;64(10):1431-46. [73 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

Guideline Developer(s)

American College of Rheumatology - Medical Specialty Society

Source(s) of Funding

Supported by a research grant from the American College of Rheumatology and by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-063120).

Guideline Committee

Task Force Panel

Composition of Group That Authored the Guideline

Panel Members: Dinesh Khanna, MD, MSc, Puja P. Khanna, MD, MPH, Blake Roessler, MD: University of Michigan, Ann Arbor; John D. FitzGerald, MD, Sangmee Bae, MD, Shraddha Prakash, MD, Marian Kaldas, MD, Maneesh Gogia, MD, Daniel E. Furst, MD, Neil Wenger, MD: University of California, Los Angeles; Manjit K. Singh, MD: Rochester General Health System, Rochester, New York; Tuhina Neogi, MD, PhD, FRCPC, Hyon Choi, MD, DrPH: Boston University Medical Center, Boston, Massachusetts; Michael H. Pillinger, MD: VA Medical Center and New York University School of Medicine, New York; Joan Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; Susan Lee, MD, Robert Terkeltaub, MD: VA Healthcare System and University of California, San Diego; Fernando Perez-Ruiz, MD, PhD: Hospital Universitario Cruces, Vizcaya, Spain; Will Taylor, PhD, MBChB: University of Otago, Wellington, New Zealand; Frédéric Lioté, MD, PhD: Université Paris Diderot, Sorbonne Paris Cité, and Hôpital Lariboisière, Paris, France; Jasvinder A. Singh, MBBS, MPH: VA Medical Center and University of Alabama, Birmingham; Nicola Dalbeth, MD, FRACP: University of Auckland, Auckland, New Zealand; Sanford Kaplan, DDS: Oral and Maxillofacial Surgery, Beverly Hills, California; Vandana Niyyar, MD, Danielle Jones, MD, FACP: Emory University, Atlanta, Georgia; Steven A. Yarows, MD, FACP, FASH: IHA University of Michigan Health System, Chelsea; Gail Kerr, MD, FRCP(Edin): Veterans Affairs Medical Center, Washington, DC; Charles King, MD: North Mississippi Medical Center, Tupelo; Gerald Levy, MD, MBA: Southern California Permanente Medical Group, Downey; N. Lawrence Edwards, MD: University of Florida, Gainesville; Brian Mandell, MD, PhD: Cleveland Clinic, Cleveland, Ohio; H. Ralph Schumacher, MD: VA Medical Center and University of Pennsylvania, Philadelphia; Mark Robbins, MD, MPH: Harvard Vanguard Medical Associates/Atrius Health, Somerville, Massachusetts

Financial Disclosures/Conflicts of Interest

Managing Perceived Potential Conflicts of Interest (COI)

Perceived potential COI was managed in a prospective and structured manner. Specifically, all participants intellectually involved in the project, whether authors or not, were required to fully and prospectively disclose relationships with pharmaceutical companies with a material interest in gout (see Supplemental Figure 2 and Appendix A, available in the online version of the original guideline document at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). Disclosures were updated every 6 months, and for the principal investigators, core expert panel (CEP), and task force panel (TFP), updated just prior to the face-to-face meeting. A summary listing of all perceived potential COI was disseminated to all participants in the project. Based on the policies of the American College of Rheumatology (ACR), which are aligned with those of many medical societies, no more than 49% of the project participants could have a COI at any given time. It was required that the project principal investigator remain without perceived potential COI prior to and during the process.

Dr. Dinesh Khanna has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Novartis and Ardea and (more than \$10,000 each) from Takeda and Savient, and has served as a paid investment consultant for Guidepoint. Dr. Puja P. Khanna has received speaking fees (less than \$10,000) from Novartis and (more than \$10,000) from Takeda, and has served on the advisory board for Novartis. Dr. Pillinger has received speaking fees and/or honoraria (less than \$10,000 each) from the RA Investigator Network, NY Downtown Hospital, Winthrop Hospital, and Einstein College of Medicine. Dr. Perez-Ruiz has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Novartis, Menarini, and Savient, and (more than \$10,000) from Ardea. Dr. Lioté has received consultant fees, speaking fees,

and/or honoraria (less than \$10,000 each) from Novartis Global, Novartis France, and Ipsen, and has served as a paid investment consultant for Gerson Lehrman Group. Dr. Choi has served on the advisory boards (less than \$10,000 each) for Takeda, URL, and Savient. Dr. Singh has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Ardea, Savient, Allergan, and Novartis, and (more than \$10,000) from Takeda, and has received investigator-initiated grants from Takeda and Savient. Dr. Dalbeth has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Takeda, Ardea, and Novartis, has received research funding from Fonterra, and holds a patent from Fonterra for milk products for gout. Dr. Niyar has received honoraria (less than \$10,000) from the American Society of Nephrology. Dr. Kerr has served as a study investigator (more than \$10,000 each) for Savient and Nuon. Dr. Edwards has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Savient, Takeda, Ardea, and Regeneron, and (more than \$10,000) from Novartis, and has given expert testimony for Novartis. Dr. Mandell has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Savient, Novartis, and Pfizer. Dr. Schumacher has received consultant fees (less than \$10,000 each) from Pfizer, Regeneron, West-Ward, and Ardea, and (more than \$10,000) from Novartis. Dr. Terkeltaub has received consultant fees (less than \$10,000 each) from Takeda, Savient, Ardea, BioCryst, URL, Regeneron, Pfizer, Metabolex, Nuon, Chugai, EnzymeRx, Ajanta, Anadys, Celgene, Isis, and Prescription Solutions, and (more than \$10,000) from Novartis, has received grant support from the VA San Diego Healthcare System and the National Institutes of Health (NIH), and has served as a paid investment consultant for Leerink Swann, Medacorp, and Guidepoint.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [American College of Rheumatology Web site](#) .

Availability of Companion Documents

Supplemental figures and Appendix A are available from the [Arthritis Care and Research Web site](#) .

Patient Resources

The following is available:

- Gout. 2012 Sep. 5 p. Available in PDF in [English](#) and [Spanish](#) from the American College of Rheumatology (ACR) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on December 27, 2012. The information was verified by the guideline developer on January 17, 2013.

Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse^{â„¢} (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the [NGC Inclusion Criteria](#).

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.